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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,775	06/23/2000	Neil R. Cashman	50111/002002	9735

21559 7590 01/20/2004

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/602,775	CASHMAN ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-82* is/are pending in the application.

4a) Of the above claim(s) *18-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17, 80-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10102003*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Amendment filed October 10, 2003 in response to the Office Action of April 9, 2003 is acknowledged and has been entered. Claims 1-17, 80 and newly added claims 81 and 82 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Specification

The Office acknowledges the changes to the title of the invention.

Drawings

The Office acknowledges the submission of the corrected drawings with the October 10, 2003 response to the Office Action of April 9, 2003.

Claim Rejections - 35 USC § 112

The rejection of claims 2 and 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to define what is meant by the phrase "does not substantially bind PrP^{C}" **is withdrawn** in view of Applicants amendment to the claims canceling the term "substantially binding" from the claim. However, the newly amended claims which now includes the term "specifically binds" remains indefinite see new rejection below.

Claim Rejections - 35 USC § 102

The rejection of claims 1-8, 10-17, 80 and newly added claims 81 and 82 under 35 U.S.C. 102(b) as being anticipated by Korth et al. (Nature, 1997, IDS Paper No. 7) **is maintained** for reasons of record.

Applicants' arguments have been fully considered but fail to persuade. Applicants arguments are that the 6H4 antibody, which was not deemed in the prior art references to preferentially bind the PrP^{Sc}, has a different binding profile as compared to the instantly claimed antibodies that bind to a YYX epitope in the context of a mammalian PrP^{Sc}. Applicants argue that the 15B3 antibody of the prior art recognizes a 3 dimensional structure, which comprises the YYR epitope. The claims are not limited to the recognition of a simple linear YYX epitope, the antibody must recognize the epitope in the context of a mammalian PrPSc particle. The prior art antibody 15B3 recognizes YYX in the context of the PrPSc particle as shown by the epitope mapping which utilizes linear peptides in the assay. Applicants attempt to further distinguish the 15B3 antibody from the instantly claimed antibodies, by indicating that the 15B3 antibody purportedly is an IgM antibody and that the 15B3 antibody is according to applicants a "low affinity" antibody. Applicant make this assertion merely because the prior art does not specifically state that the antibody is a "high affinity" antibody. First of all the instantly claimed antibodies are not limited to an IgG antibody type (see claim 8 of the instant invention). Second, it is well established in the art that if antibodies can be used for immunoprecipitation or immunoblotting they are expected to have a binding affinity that ranges from a weak signal [10^{-6} M] to a strong signal [10^{-9} M], since the 15B3 antibodies of the prior art have been used for immunoprecipitation and immunoblotting the 15B3 antibody would fall within the binding

affinity of the instantly claimed invention. The "high binding" affinity as claimed in the instant invention is defined in the specification on page 8, lines 13-15, as ranging from less than 10 μM [10^{-5} M] to less than 10 nM [10^{-8} M], the art would recognize this to encompasses everything from a weak signal to a strong signal. Therefore, the limitation "high binding affinity" does not help define the antibodies of the instant invention over the prior art antibody.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the antibody limited to an IgG antibody; that the antibody recognize a simple linear epitope) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants are arguing that the process of producing the antibody, i.e. using a whole prion particle (prior art) vs. a simple linear epitope (instant invention) produces antibodies that recognize distinctly different features of the PrPSc. This is not convincing since the disease form PrPSc and the cellular form PrPC have the same amino acid sequence, antibodies that can distinguish between the two forms must be able to distinguish a structural conformer that is present in one structure and absent in the other structure. From the crystal structure of the prion protein disclosed in the prior art the YYX epitopes are present on the surface of the PrPSc disease conformer. The 15B3 antibody recognize a YYR epitope in the context of a mammalian PrPSc structure, in order to anticipate the instant claim the antibody needs to bind the YYX epitope with an affinity constant of 10^{-5} M which is an order of magnitude weaker than what the prior art would consider to be weak antibody binding. Since the antibody of the prior art recognizes the same PrPSc structure and has

been shown to also recognize a YYX epitope containing epitope within the context of structure, one of ordinary skill in the art would expect the antibody to also interact with a peptide containing the YYX epitope especially since the interaction does not have to be very strong. The interaction would only need to be 10^{-5} M, which the prior art would consider to be an order of magnitude weaker than a weak binding antibody, yet the definition of the instant invention would encompass this to be considered "high affinity" binding. The addition of cysteine residues to peptides contain the YYX epitope would not be expected to effect the binding to the epitope since the cysteine is not found in the natural structure and has been added merely as a tool to link the peptide to a carrier molecule.

Applicants have indicated that the 15B3 antibody when compared to the antibodies of the instant invention would have different binding profiles [see response page 23 and 24]. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant [*In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). See MPEP 716.01(c)]. The arguments of counsel cannot take the place of evidence in the record [*In re Schulze* , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C)].

The claims are directed to antibodies that bind with "high binding" affinity to a YYX epitope. The specification defines "high binding affinity" on page 8, lines 13-15, as ranging from less than 10 μM [10^{-5} M] to less than 10 nM [10^{-8} M]. The prior art recognizes that binding constant of 10^{-6} M would be considered a weak signal and a binding constant of 10^{-8} M

would be considered a strong signal. Therefore term "high affinity" provides a wide range of binding affinities but does not help distinguish an antibody which has a weak binding affinity constant from a high binding affinity constant because the term as defined in the specification would include both. Because the instantly claimed antibodies recognize the disease form PrPSc which does not contain a cysteine residue next to the YYX epitope the additional cysteine in the claimed peptides do not add to the antibody recognition of PrPSc. To fall within the claimed scope of the invention the antibody only needs to bind at an affinity of 10^{-5} M which is on order of magnitude weaker than what is recognized in the art as weak binding antibody.

Korth et al. disclose monoclonal antibodies 15B3 recognize a YYX epitope (see figure 2), the reference discloses hybridoma cell lines for the production of the antibodies. The 15B3 antibody binds selectively to the PrP^{Sc} from various species without the need to digest the sample with proteinase K (see page 77, last paragraph). The reference discloses immunoprecipitation experiments (see figure 1 and 2; page 77 characterization of antibodies) indicating that the antibody binding range of the antibody is between 10^{-6} M between 10^{-8} M. Therefore, the rejections are maintained as being anticipated by Korth et al.

The rejection of claims 1-17, 80 and newly added claims 81 and 82 under 35 U.S.C. 102(a) as being anticipated by Korth et al. (WO 98/37210, see IDS) or under 35 U.S.C. 102(b) by Korth et al. (EP 0 861 900, see IDS) **is maintained** for reasons of record.

Applicants' arguments have been fully considered but fail to persuade. Applicants arguments are that the 6H4 antibody, which was not deemed in the prior art references to preferentially bind the PrP^{Sc}, has a different binding profile as compared to the instantly claimed

antibodies that bind to a YYX epitope in the context of a mammalian PrP^{Sc}. Applicants argue that the 15B3 antibody of the prior art recognizes a 3 dimensional structure, which comprises the YYR epitope. The claims are not limited to the recognition of a simple linear YYX epitope, the antibody must recognize the epitope in the context of a mammalian PrPSc particle. The prior art antibody 15B3 recognizes YYX in the context of the PrPSc particle as shown by the epitope mapping which utilizes linear peptides in the assay. Applicants attempt to further distinguish the 15B3 antibody from the instantly claimed antibodies, by indicating that the 15B3 antibody purportedly is an IgM antibody and that the 15B3 antibody is according to applicants a "low affinity" antibody. Applicant make this assertion merely because the prior art does not specifically state that the antibody is a "high affinity" antibody. First of all the instantly claimed antibodies are not limited to an IgG antibody type (see claim 8 of the instant invention). Second, it is well established in the art that if antibodies can be used for immunoprecipitation or immunoblotting they are expected to have a binding affinity that ranges from a weak signal [10^{-6} M] to a strong signal [10^{-9} M], since the 15B3 antibodies of the prior art have been used for immunoprecipitation and immunoblotting the 15B3 antibody would fall within the binding affinity of the instantly claimed invention. The "high binding" affinity as claimed in the instant invention is defined in the specification on page 8, lines 13-15, as ranging from less than 10 μM [10^{-5} M] to less than 10 nM [10^{-8} M], the art would recognize this to encompasses everything from a weak signal to a strong signal. Therefore, the limitation "high binding affinity" does not help define the antibodies of the instant invention over the prior art antibody.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the

antibody limited to an IgG antibody; that the antibody recognize a simple linear epitope) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants are arguing that the process of producing the antibody, i.e. using a whole prion particle (prior art) vs. a simple linear epitope (instant invention) produces antibodies that recognize distinctly different features of the PrPSc. This is not convincing since the disease form PrPSc and the cellular form PrPC have the same amino acid sequence, antibodies that can distinguish between the two forms must be able to distinguish a structural conformer that is present in one structure and absent in the other structure. From the crystal structure of the prion protein disclosed in the prior art the YYX epitopes are present on the surface of the PrPSc disease conformer. The 15B3 antibody recognize a YYR epitope in the context of a mammalian PrPSc structure, in order to anticipate the instant claim the antibody needs to bind the YYX epitope with an affinity constant of 10^{-5} M which is an order of magnitude weaker than what the prior art would consider to be weak antibody binding. Since the antibody of the prior art recognizes the same PrPSc structure and has been shown to also recognize a YYX epitope containing epitope within the context of structure, one of ordinary skill in the art would expect the antibody to also interact with a peptide containing the YYX epitope especially since the interaction does not have to be very strong. The interaction would only need to be 10^{-5} M, which the prior art would consider to be an order of magnitude weaker than a weak binding antibody, yet the definition of the instant invention would encompass this to be considered "high affinity" binding. The addition of cysteine residues to peptides contain the YYX epitope would not be expected to effect the binding to the

epitope since the cysteine is not found in the natural structure and has been added merely as a tool to link the peptide to a carrier molecule.

Applicants have indicated that the 15B3 antibody when compared to the antibodies of the instant invention would have different binding profiles [see response page 23 and 24]. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant [*In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). See MPEP 716.01(c)]. The arguments of counsel cannot take the place of evidence in the record [*In re Schulze* , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C)].

The claims are directed to antibodies that bind with "high binding" affinity to a YYX epitope. The specification defines "high binding affinity" on page 8, lines 13-15, as ranging from less than 10 μM [10^{-5} M] to less than 10 nM [10^{-8} M]. The prior art recognizes that binding constant of 10^{-6} M would be considered a weak signal and a binding constant of 10^{-8} M would be considered a strong signal. Therefore term "high affinity" provides a wide range of binding affinities but does not help distinguish an antibody which has a weak binding affinity constant from a high binding affinity constant because the term as defined in the specification would include both. Because the instantly claimed antibodies recognize the disease form PrPSc which does not contain a cysteine residue next to the YYX epitope the additional cysteine in the claimed peptides do not add to the antibody recognition of PrPSc. To fall within the claimed

scope of the invention the antibody only needs to bind at an affinity of 10^{-5} M which is on order of magnitude weaker than what is recognized in the art as weak binding antibody.

Korth et al. disclose monoclonal antibodies 15B3 and 6H4 that recognize a YYX epitope, the reference discloses hybridoma cell lines for the production of the antibodies (see claim 1, 2, 8, 10). The 15B3 antibody binds selectively to the PrP^{Sc} from various species without the need to digest the sample with proteinase K . The reference discloses immunoprecipitation experiments (see claim 25) and the compositions required for carrying out these experiments as well as kits. In the reference 0/0 mice were injected with prion protein in which comprise the YYR epitope located on the outside of the molecule (see claim 22) therefore the antibodies generated by the mouse are polyclonal antibodies against a YYR epitope. The office does not have laboratory facilities to test whether the antibodies of the prior art which bind a YYX epitope will also bind the YYX epitope found in SEQ ID NO: 32 or 33. The reference also discloses using the antibody as therapeutic agents (see WO 98/37210 page 22). Therefore, the instant invention is anticipated by Korth et al.

New rejection in view of Applicant's amendment to the claims:

Claims 2 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended the claims from reading "does not substantially bind" to "does not specifically bind" in the amendments of October 10, 2003. In response to applicant's arguments the claims fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the antibody does not

discriminate PrP^{C} from PrP^{Sc}; that the antibodies bind to disease specific prion-protein and not normal prion protein) are not recited in the rejected claim(s). In an attempt to clarify what is encompassed by the claim applicants are trying distinguish between "high affinity" and "low affinity" binding (i.e. does not specifically bind). However, the specification defines "high binding affinity" on page 8, lines 13-15, as ranging from less than 10 μM [10^{-5} M] to less than 10 nM [10^{-8} M]. The art generally recognizes that a binding affinity of 10 μM [10^{-5} M] would be considered a weak interaction [see table 3.1 in Harlow et al., Antibodies: a laboratory manual, Cold Spring Harbor Laboratory (1988) page 27-28]. Based on the definition provided in the specification the "high affinity" binding encompasses binding affinities that the ordinary artisan would recognize as being a weak antibody binding interaction falling within the term "does not specifically bind". Therefore the claims remain indefinite because it is not clear what is encompassed by the term "does not specifically bind" especially when read in view of the definition of what constitutes a "high binding affinity" antibody.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 1/9/04